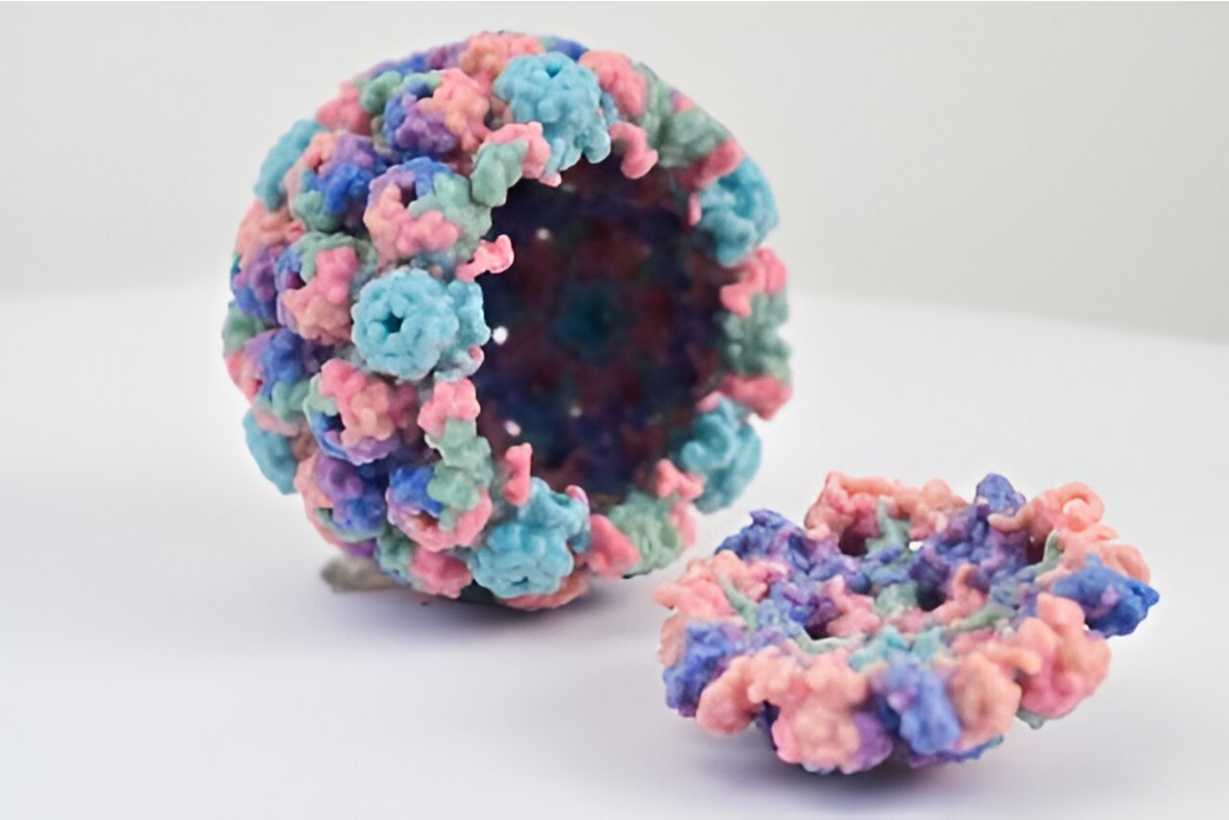
Cellular DNA damage response pathways might be useful against some disease-causing viruses

August 21 2024, by Ellen Goldbaum



The UB research is applicable to two types of small DNA viruses: papillomaviruses, such as HPV, and polyomaviruses, such as the one shown here in a 3D print. Polyomaviruses infect most people without causing serious disease but they can lead to serious diseases and some cancers in immunologically weakened individuals. Credit: NIAID

New research reveals that triggering a cell's DNA damage response could be a promising avenue for developing novel treatments against several rare but devastating viruses for which no antiviral treatments exist, possibly including human papilloma virus (HPV), which causes cancer.

Published online on Aug. 10 in *Nucleic Acids Research*, the paper focuses on the DNA damage response pathway and demonstrates how this pathway can reduce the function of a viral enzyme, a helicase, resulting in suppressing viral replication.

"This research is significant both for understanding how cells respond to DNA damage, to prevent them from becoming cancerous in the first place, how targeting this pathway can be used in new cancer treatments, and because it now opens up possibilities for new approaches to treating some rare but devastating viral infections," says Thomas Melendy, Ph.D., senior author on the paper and associate professor of microbiology and immunology in the Jacobs School of Medicine and Biomedical Sciences at the University at Buffalo.

How replication slows in response to DNA damage

The research focuses on a process called the DNA damage response, part of which has evolved to stop or slow DNA synthesis whenever cellular DNA damage occurs.

"These pathways are important for preventing exacerbation of DNA damage that can lead to either cell death or cancer," explains Rama Dey-Rao, Ph.D., research assistant professor of microbiology and immunology in the Jacobs School and joint first author on the paper with Caleb Hominski, Ph.D., a previous student in the lab.

When these pathways are activated, DNA replication is suppressed at

sites in the genome called origins; at the same time, the progression of DNA replication forks also slows down. Replication forks, so-called because their structure resembles a fork, are where large groups of proteins coordinate genome replication through the unwinding and synthesis of DNA.

Melendy says that while quite a bit is known about how DNA damage response causes cells to stop DNA replication origins from "firing," it's been much harder to figure out how the progression of replication forks slows down in response to DNA damage.

"Researchers have been very interested in how that slowing occurs because it's so dramatic," says Melendy. "DNA damage response pathways cause replication forks to slow down progression by about ten-fold. This ten-fold slowdown means that synthesis of the cell's genome, which usually takes about 12 hours, would take nearly five days, greatly increasing the time cells have to repair DNA damage."

A viral connection

For years, Melendy and his colleagues have been studying two types of small DNA viruses: papillomaviruses, such as HPV, and polyomaviruses, which infect most people without causing serious disease but can lead to serious diseases and some cancers in immunologically weakened individuals. A rare cancer caused by a polyomavirus caused the death of musician Jimmy Buffett in 2023.

"We previously showed that in response to DNA damage, HPV does not stop or slow its DNA replication, while polyomaviruses do stop or slow their DNA replication," says Melendy, "so by comparing and contrasting these two virus types we can gain insights into how polyomavirus DNA replication is slowed in response to DNA damage, which in turn provides us insights into how human cells slow replication forks."

In the current research, they demonstrate that a phosphorylation site—where a phosphate is added to a molecule—on the major polyomavirus DNA replication and transcription protein is highly conserved in polyomaviruses across many animal species.

"The conservation of this phosphorylation/modification across polyomaviruses that have evolved to infect many different species of mammals suggested it was likely important," says Melendy.

To study the effects of this, the UB researchers made a mutation at the specific amino acid residue on the viral protein where this phosphorylation occurs to mimic the addition of a phosphate group being there.

When they expressed this mutant viral protein in human cells using a system to evaluate polyomavirus DNA replication, they found the virus's genome replication was decreased by 10-fold. However, viral transcription was unaffected, indicating that phosphorylation on that amino acid residue has a highly specific effect on viral DNA replication, but didn't affect other functions of that protein.

The role for DNA helicase

In comparing the wild-type and mutant proteins, they found the only function it was compromised for was the ability to act as a DNA helicase, unwinding DNA strands to facilitate entry of DNA synthesis enzymes.

"This is the first demonstration that it might be possible to use phosphorylation as a 'switch' on a DNA helicase to dial down replication speed," explains Melendy.

Evidence suggests a similar phosphorylation can occur in human DNA

helicases as well.

"For many cancers, if we selectively inhibit the DNA damage checkpoints they still retain, and simultaneously treat with lower than normal amounts of DNA-damaging chemotherapeutics, then we might be able to selectively damage cancer cells while leaving non-cancerous cells intact, greatly enhancing cancer cell killing while simultaneously reducing toxic side effects."

This is an ongoing area of study by the UB researchers with their collaborators at Roswell Park Comprehensive Cancer Center.

Based on the current study, these DNA damage checkpoints may now be relevant to treating viral infections of the small DNA viruses under investigation at UB.

"Because they rely almost exclusively on host cell enzymes to synthesize their viral genomes, these small DNA viruses have been very resistant to anti-viral therapeutics," says Melendy.

"We currently have no antiviral treatments for HPV or polyomaviruses. By triggering the DNA damage response in a patient, this could dramatically slow viral DNA replication, suppressing the infection, providing us with a novel avenue for possible antiviral treatments of these as-of-yet untreatable viral infections."

More information: Caleb Homiski, et al. DNA damage-induced phosphorylation of a replicative DNA helicase results in inhibition of DNA replication through attenuation of helicase function. *Nucleic Acids Research*(2024). DOI: 10.1093/nar/gkae663

Provided by University at Buffalo